PATENT

Attorney Docket 221904-1030

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

Applicant:	Wayne R. Danter *et al.*	:	Paper No.:
Serial No.	10/531,107	:	Group Art Unit: 1624
Filed:	November 7, 2005	:	Examiner: Deepak R. Rao
For:	**Protein Tyrosine Kinase Inhibitors**		

DECLARATION UNDER 37 C.F.R. 1.132

Box Fee Amendment
Commissioner for Patents
Washington, DC 20231

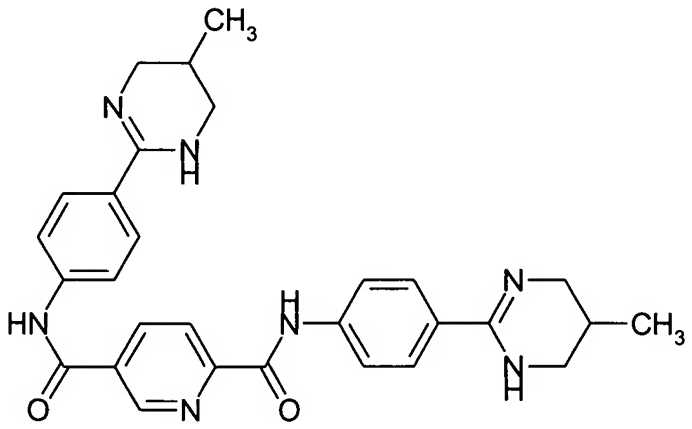
I, Dr. Wayne R. Danter, do hereby declare and say as follows:

1. I obtained a Doctorate in Medicine (MD) from the University of Western Ontario in London, Canada, in **1979**. After completing a residency training program in Internal Medicine and post doctoral research training in Clinical Pharmacology, I became an Assistant Professor in the Department of Medicine at the University of Western Ontario in July, **1987**. I was promoted to Associate Professor of Medicine in **1997**. In addition to teaching, my clinical focus was in general Cardiology, Cardiovascular Diseases associated with HIV, and Cardiovascular Risk Management. I conducted my research into the application of Artificial Intelligence (AI) models to (1) disease diagnosis, (2) therapeutic outcome prediction, and (3) computational Structure Activity Relationships (SAR) beginning in 1988. My primary research focus was on predicting specific relationships between molecular structure and biological activity in order to discover potential new treatments for cancers and HIV. While at the University of Western Ontario, I authored several peer reviewed journal publications and delivered a number of international conference presentations in this field. My research eventually resulted in a proprietary process called CHEMSAS™ that is used to predict specific biological activities of therapeutic candidates based on their chemical structure. CHEMSAS is based on a very straightforward process. The traditional drug discovery

process was first decomposed into its most basic elements. A computer simulation was then developed and validated for each individual basic element. Finally the individual validated computational elements were reassembled in to a multi-step process. CHEMSAS is currently able to produce a detailed molecular profile by making predictions about targeted efficacy, physical chemical and general ADMET properties. This computational molecular profile can be combined with human expertise to select molecules for synthesis, patenting and preclinical development. Although not extensively published, this process has been used in developing a number of candidate therapeutic molecules which are the subject of at least the following US patent applications: 10/531,107; 60/416,911; 10/522,944; 60/399,408; 60/884,489; 60/907,285; 12/013,079; 60/884,504; 61/081,676; 61/006,150. In 1999, I founded Critical Outcome Technologies, Inc. (COTI) to further develop and commercialize the CHEMSAS™ process. I currently hold the positions of President, Chief Scientific Officer, and Director of COTI. Based on my education and work experience, I consider myself well-trained in cancer biology, and specifically in tyrosine kinase-based cancer research.

2. I am a named inventor on the above-referenced patent application and am familiar with the contents thereof. I have been advised that the USPTO has rejected one or more independent claims presently pending in the above-identified patent application, based on an alleged finding of nonenablement.

3. The method for treatment of cancer of the above-referenced patent application comprises the administration of the formulae of the above-referenced patent application, including amongst other compounds, the compound of Formula II, which is indicated as COTI-001. This formula is reproduced below:



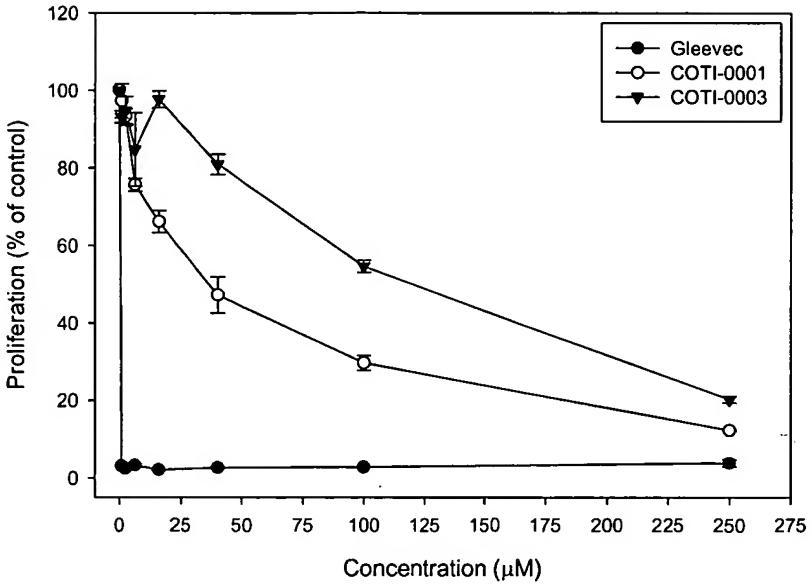
Formula II

4. As described on page 27, lines 21-28, of the description, compounds with potential tyrosine kinase activity were analyzed in a validated computational (*in silico)* assay that is based on public domain National Cancer Institute *in vitro* anti-cancer data. The compounds were first decomposed to 110 descriptors using the proprietary CHEMSAS® algorithm. This decomposition process resulted in a molecular data pattern of 110 variables that was then input into the *in silico* model. The output of the model is a prediction of the -Log(GI50) for the compound(s) being analyzed against the specific cancer cell type in question. The *in silico* data found in Table 1, on page 28 of the description, clearly predicts that compounds of Formula I, particularly the compound of Formula II (designated COTI-001), are effective at inhibiting the growth of a variety of cancer cells of different origin, including leukemias, lung cancers, colon cancers, CNS cancers, melanomas, ovarian cancers, renal cancers, prostate cancers, and breast cancers. The *in silico* predictions are validated with *in vitro* data in Example 2.

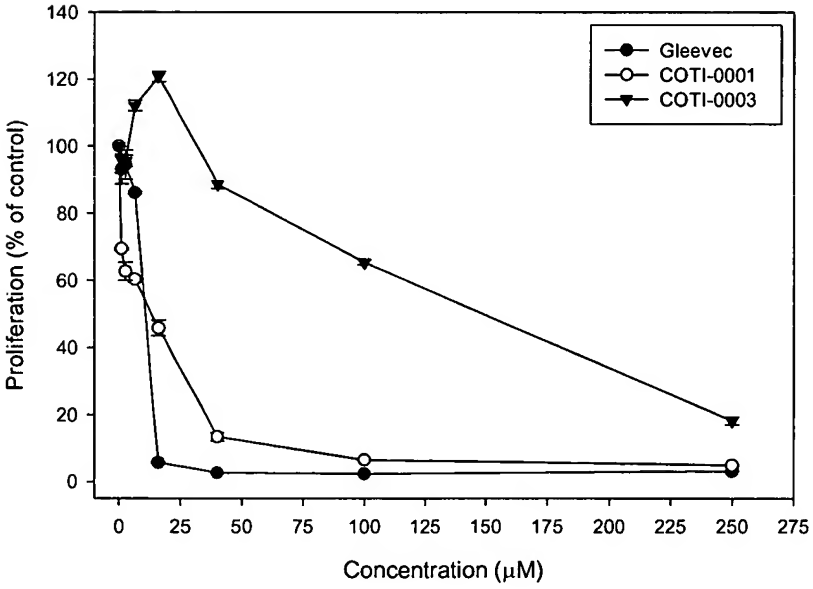
5. The CHEMSAS® platform provides a means of determining, predicting and/or testing the properties of a compound, particularly when used to determine the properties of compounds according to the above-referenced patent application. By demonstrating *in vitro* that COTI-001 has activity against a number of additional cell types listed in Table 1, on page 28 of the description, the predictive value of the *in silico* data is further validated and extended to additional cancer types.

6. Further *in vitro* data is provided in the graphs and tables found below. This data shows the results of treatment of different cell types with COTI-001 or Gleevec™. Gleevec™ is a 2-phenylaminopyrimidine derivative which functions as an inhibitor of inappropriate tyrosine kinase activity. The cell types tested and shown in the data below include human K562 leukemia cells, murine P388D1 acute myelogenous leukemia cells, human MCF-7 breast cancer cells, human DMS114 lung cancer cells, human HT-29 colon cancer cells, human HL-60 acute promyelocytic leukemia cells, murine L1210 lymphocytic leukemia cells, and human THP-1 acute monocytic leukemia cells.

Cell Proliferation Assay of K562 cells
testing 3 different compounds - June 6 03

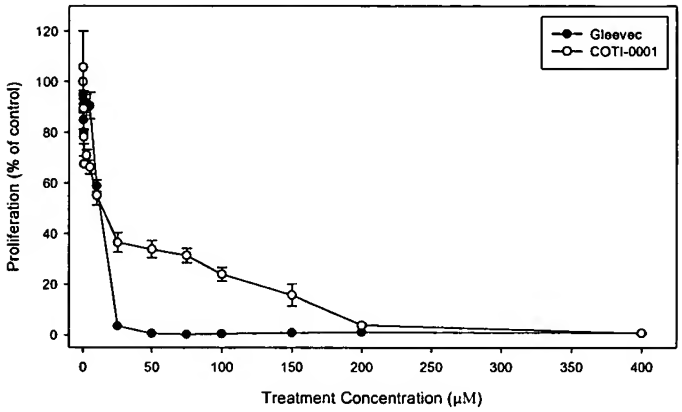


Cell Proliferation Assay of P388D1 cells
testing 3 different compounds - June 6 03

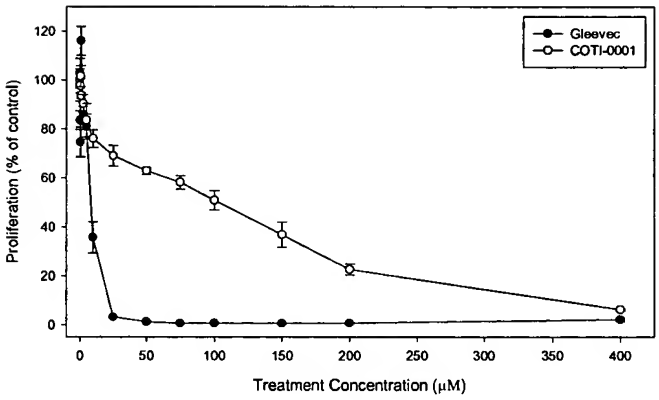


DAY	12	14	16	19	21	23	26	27	29	32	39
Control tumours	0 0513	0.067	0.067	0 0670	0.0848	0.0945	0.1047	0.1346	0.1346	0.0916	0.1047
treated with vehicle	0	0	0 0236	0.0916	0.0628	0.0503	0.0503	0.0636	0.0503	0.0636	0.0916
(volume estimated by the formula:	0.0385	0.0503	0.0742	0.1047	0.1047	0.1267	0.1267	0.1346	0.1346	0.1267	0.0916
volume = length × width2 × °/6)	0.0192	0 0188	0.0385	0.0545	0.0545	0.0836	0 0636	0.0704	0.0851	0.0916	0.1109
injected with vehicle on days 2,5, 7,9,12,14,16,19,21	0 0141	0.0141	0.0188	0.0236	0.0503	0.0545	0.0545	0 0503	0.0503	0.0851	0.0916
after injection of MCF-7 tumour cells	0.0321	0.0545	0.0586	0 0586	0.0848	0.0795	0 0628	0.0795	0.0636	0 0916	0.0982
	0.0424	0.0236	0.0236	0.0321	0.0321	0.0377	0.0377	0.0477	0 1131	0.0871	0.0871
	0	0	0.0786	0.0785	0.0586	0.0503	0.0503	0.0851	0.0851	0.0503	0.0786
Mean volume (cubic cm)	0.0247	0.0285	0.0479	0.0638	0.0666	0.0696	0.0688	0.0832	0.0896	0.0859	0.0943
Standard error	0.0069	0.0091	0.0087	0.0098	0.0082	0.0104	0.0108	0.0121	0.0123	0.0079	0.0036
Gleevec-treated tumours	0	0	0	0	0	0	0	0 0165	0 0165	0.0335	0.0377
12.5 mg/kg	0	0.0189	0.0461	0.0257	0.0419	0.053	0.053	0.0477	0.053	0.0419	0.0655
injected with drug on days 2,5, 7,9,12,14,16,19,21	0.0477	0.0419	0.0503	0 0785	0.0838	0.1131	0.1131	0 1225	0.1319	0.132	0.2053
after injection of MCF-7 tumour cells	0	0.0283	0.0503	0 0236	0 0586	0.0545	0.0545	0.0851	0.0851	0.0785	0.0461
	0.0321	0.0419	0.0545	0.0532	0.0419	0.0655	0.0655	0	0	0	0
	0	0.0377	0.0586	0.0334	0.0503	0.0503	0.0503	0.0689	0.0689	0.0851	0.1508
	0	0	0	0.0321	0	0.0063	0.0063	0.0655	0.053	0.0655	0.0785
	0.0377	0.0419	0.0189	0.072	0.0503	0.1131	0 1131	0.1131	0.1109	0.1131	0 1131
	0.0289	0.0503	0.0256	0.0503	0.103	0.0851	0.0851	0.095	0.095	0.0655	0.0655
Mean volume (cubic cm)	0.0163	0.029	0.0338	0.041	0.0455	0.0601	0.0601	0.0683	0.0683	0.0683	0.0847
Standard error	0.0067	0.0063	0.0077	0.0083	0.0105	0.0134	0.0126	0.0138	0.043	0.0135	0.0209
Gleevec-treated tumours	0	0	0	0	0	0.0103	0 0105	0.0105	0.0105	0	0
25 mg/kg	0.0321	0 0419	0.0545	0.0532	0.0419	0.0655	0.0655	0	0	0	0
injected with drug on days 2,5, 7,9,12,14,16,19,21	0	0	0	0	0.0114	0.0204	0 02	0.0215	0 0105	0	0
after injection of MCF-7 tumour cells	0.0221	0.0354	0.0361	0.0571	0.0558	0.0561	0.0467	0.0416	0.0105	0	0
	0	0	0 0352	0.0341	0.0226	0.0105	0	0	0	0	0
	0 0145	0 0115	0.0205	0.0318	0.0298	0.0215	0.0106	0	0	0	0
	0	0	0	0	0	0.0245	0 0353	0.0529	0.0858	0.0536	0.0231
	0.0111	0.0132	0.0342	0.0452	0.0499	0.0762	0.0598	0.0442	0.0442	0.0376	0.0376
	0	0.0121	0.0254	0 0277	0.0597	0.0583	0.0317	0.0222	0.0222	0.0113	0
Mean volume (cubic cm)	0.0089	0.0127	0.0229	0.0277	0.0301	0.0381	0.0313	0.0214	0.0204	0.0114	0.0067
Standard error	0.004	0.0053	0.0065	0.0076	0.0077	0.0085	0.0077	0.0069	0.0094	0.0067	0.0046
COTI-0001-treated tumours	0.0513	0.0321	0 053	0 0851	0.0503	0.0851	0.0838	0 0982	0.0916	0 0916	0.0916
0.00125 mg/kg	0.0916	0.0742	0.0335	0.0503	0.0851	0.0689	0.0689	0.0689	0 0689	0.0742	0.0851
injected with drug on days 2,5, 7,9,12,14,16,19,21	0 0628	0.0503	0.0283	0.0503	0.0636	0.1047	0.1047	0.0916	0.0916	0.0916	0.0916
after injection of MCF-7 tumour cells	0	0.0257	0.0586	0.0916	0.1113	0.1047	0.1047	0.1047	0.1047	0.0742	0.1113
	0.0545	0.0449	0.0321	0 0848	0.1047	0.067	0.067	0.0586	0 0503	0.0503	0.0785
	0	0	0	0.0785	0.0857	0.0636	0.0636	0 0848	0.0982	0 1508	0 1508
	0.0098	0.0189	0 0655	0.0419	0.0419	0.053	0.053	0.053	0.0636	0.0503	0.0785
	0 0073	0.0189	0 0189	0.0257	0.0419	0.0257	0.0257	0.0419	0.053	0.0785	0.0785
Mean volume (cubic cm)	0.0347	0.0331	0.0362	0.0635	0.0731	0.0716	0.0714	0.0752	0.0777	0.0827	0.0957
Standard error	0.0123	0.0081	0.0077	0.0086	0.0097	0.0094	0.0093	0.0081	0.0075	0.0112	0.0088

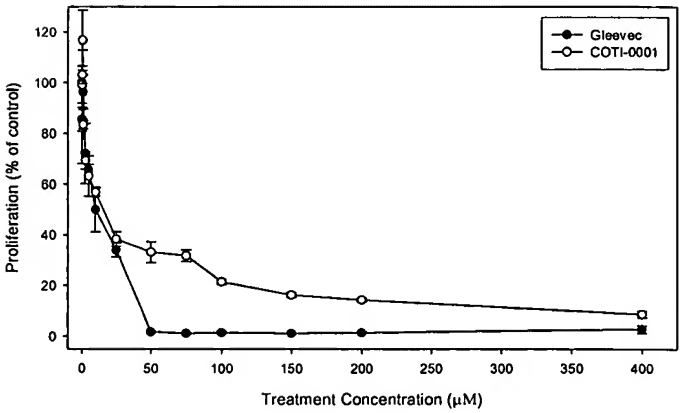
Proliferation Assay of DMS114 cells treated with
Gleevec or COTI-0001 - Aug. 27 2003



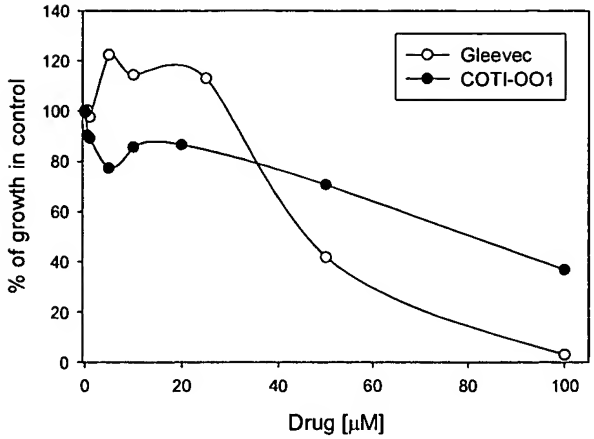
Proliferation Assay of HT-29 cells treated with
Gleevec or COTI-0001 - Aug. 27 2003



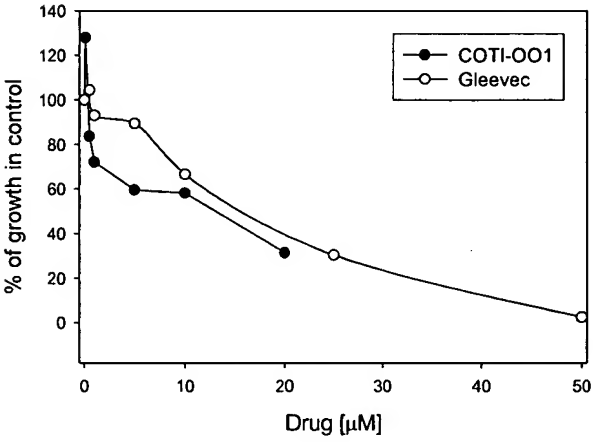
Proliferation Assay of MCF-7 cells treated with
Gleevec or COTI-0001 - Aug. 27 2003



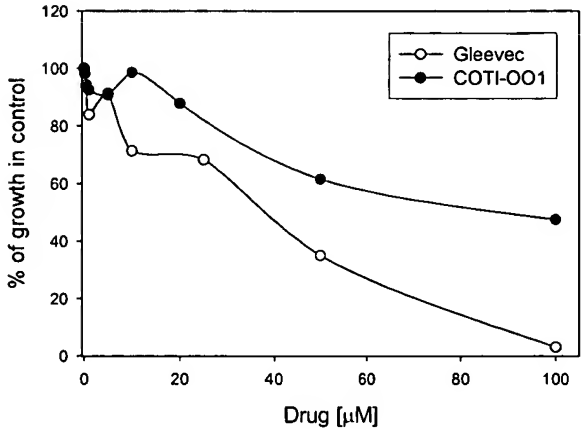
COTI-OO1 or Gleevec
Human HL-60 cells derived from acute promyeolocytic leukemia



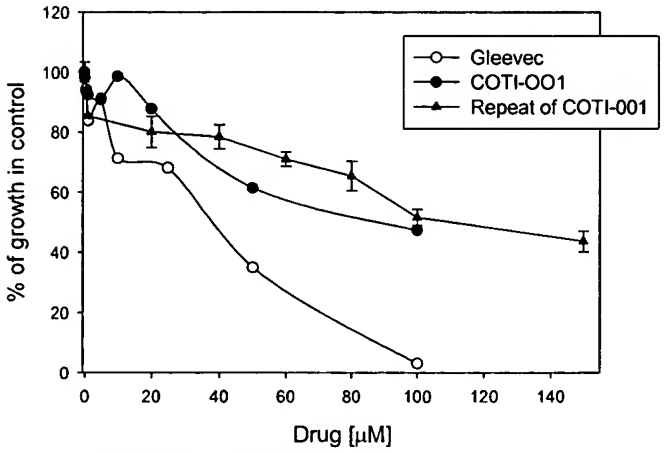
COTI-OO1 or Gleevec
Mouse L1210 cells derived from lymphocytic leukemia



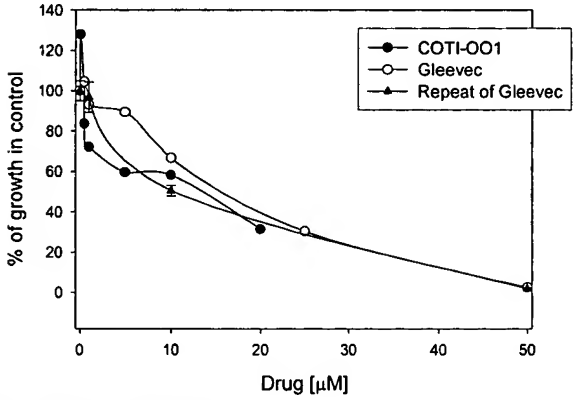
COTI-OO1 or Gleevec
Human THP-1 cells derived from acute monocytic leukemia



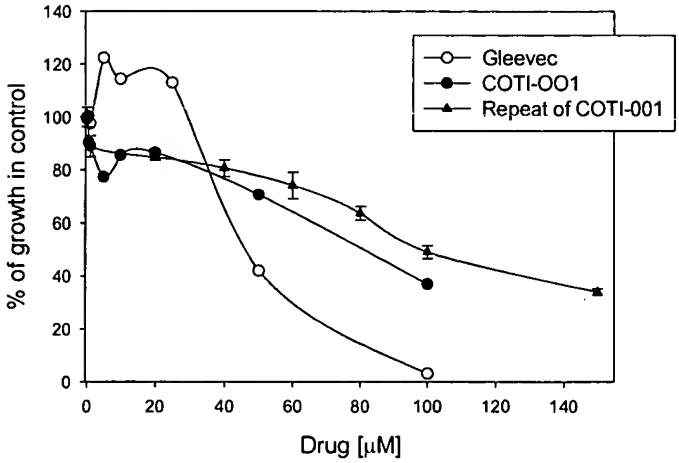
COTI-OO1 or Gleevec
Human THP-1 cells derived from acute monocytic leukemia



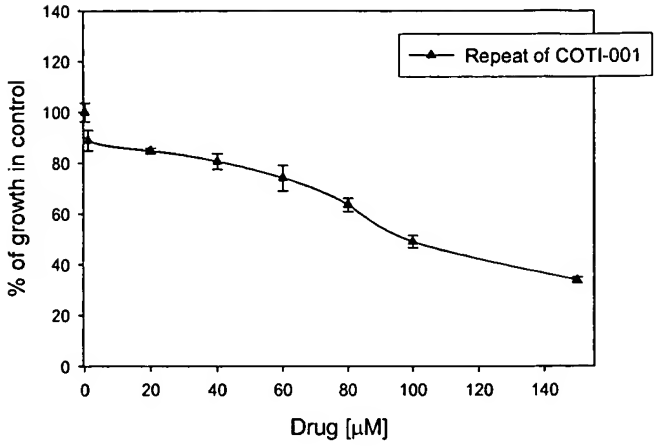
COTI-OO1 or Gleevec
Mouse L1210 cells derived from lymphocytic leukemia



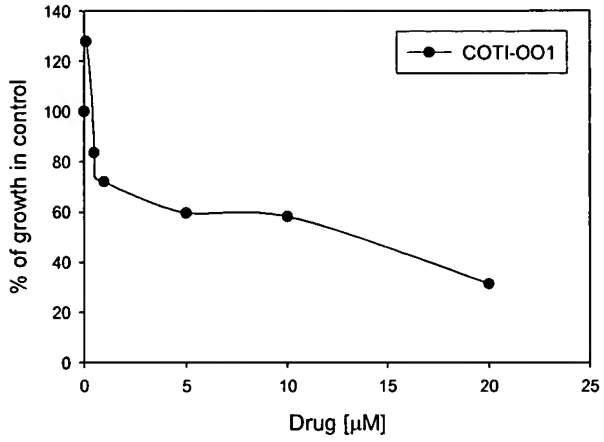
COTI-OO1 or Gleevec
Human HL-60 cells derived from acute promyeolocytic leukemia



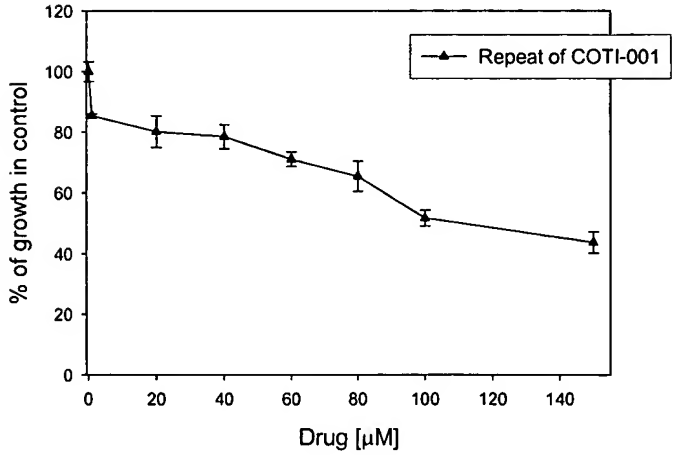
COTI-OO1
Human HL-60 cells derived from acute promyeolocytic leukemia



COTI-OO1
Mouse L1210 cells derived from lymphocytic leukemia



COTI-OO1
Human THP-1 cells derived from acute monocytic leukemia



7. The K562 cell line is described on page 27 of the description as over-expressing the abnormal protein tyrosine kinase found in Chronic Myelogenous Leukemia (CML). Referring to Table 1 on page 28 of the description and the *in vitro* confirmation thereof in Example 2, COTI-001 was effective in inhibiting growth and survival of K562 leukemia cells. It is therefore reasonable to predict that COTI-001, and comparative compounds of Formula I of the above-referenced patent application, have efficacy in the treatment of tyrosine kinase dependent cancers. Zwick *et al.* (Receptor Tyrosine Kinases as Targets for Anticancer Drugs; TRENDS in Mol. Med., 8:17-23, 2002) and Krause *et al.* (Tyrosine Kinases as Targets for Cancer Therapy; N. Engl. J. Med.; 353:172-187, 2005) list numerous tyrosine kinase dependent cancers such as breast cancers, cervical cancers, kidney cancers, pancreatic cancers, leukemias, melanomas, colon cancers, ovarian cancers, renal cancers, prostate cancers, and lung cancers. Since these articles show that these cancers are a result of inappropriate tyrosine kinase activity and are treatable using tyrosine kinase inhibitors. Hence, cancers involving inappropriate tyrosine kinase activity should be treatable by the formulae of the above-referenced patent application, including COTI-001.

8. Many references show that Gleevec™, which like the claimed compounds, functions as a tyrosine kinase inhibitor, is effective in treating a wide range of cancers *in vivo*. For example, le Coutre *et al.* (*In Vivo* Eradication of Human BCR/ABL-Positive Leukemia Cells With an ABL Kinase Inhibitor; J. Nat. Cancer Inst., 91:163-168, 1999) shows that CGP57148B (Gleevec™) prolongs tumor free survival and reduces tumor weight in mice injected with leukemia cells. Similarly, Decaudin *et al.* (*In Vivo* Efficacy of STI571 in Xenografted Human Small Cell Lung Cancer Alone or Combined with Chemotherapy; Int. J. Cancer, 113:849-856, 2005) shows that STI571 (Gleevec™) reduces tumor volume in mice bearing SCLC tumors. Additionally, Chelouche Lev *et al.* (Inhibition of Platelet-Derived Growth Factor Receptor Signaling Restricts the Growth of Human Breast Cancer in the Bone of Nude Mice; Clin. Cancer Res., 11:306-314, 2005) shows that STI571 (Gleevec™) significantly decreased tumor size in mice bearing breast cancer cell tumors. Finally, Attoub *et al.* (The c-kit Tyrosine Kinase Inhibitor STI571 for Colorectal Cancer Therapy; Cancer Res., 62:4879-4883, 2002) shows that STI571 (Gleevec™) reduced tumor volume and weight in mice bearing colorectal cancer cell tumors.

9. The cancers tested by le Coutre *et al.*, Decaudin *et al.*, Chelouche Lev *et al.*, and Attoub *et al.*, for Gleevec™ responsiveness, correspond to the cancers that were exemplified in the *in vitro* data found above, for COTI-001 responsiveness. It is notable that Gleevec™ has efficacy both *in vitro* and *in vivo* for treatment of a wide range of cancers, such as leukemia, lung cancer, breast cancer, and colorectal rectal. Since COTI-001 and Gleevec™ were exemplified in the *in vitro* experiments, as detailed above, and were found to be effective in a number of cancer cells lines, it is reasonable to predict, on the basis of the corresponding *in vivo* Gleevec™ data described in the attached references, that COTI-001 would also have comparable *in vivo* activity to treat a broad range of cancers.

10. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Wayne R. Danter

March 13/2009

Date